Kowa Research Institute, Inc.

K-161-3.01

A Phase 3, Prospective, Double-masked, Randomized, Multi-center, Vehicle-controlled, Parallel-group, 12-week Administration and 40-week Extension Study Confirming the Efficacy and Safety of K-161 Ophthalmic Solution for the Treatment of Moderate to Severe Dry Eye Disease

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Addendum to Statistical Analysis Plan

Version 1.0

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Introduction:

The objective of this Statistical Analysis Plan (SAP) addendum is to provide modifications and corrections to the final *K-161-3.01* SAP, dated May 24, 2023.

List of Modifications/Corrections to the final *K-161-3.01* SAP Dated May 24, 2023:

1. Change to per protocol set (PPS) defined in SAP Section 4.4.2

PPS is redefined to exclude subjects with major protocol deviations (PDs) related to primary and key secondary endpoints, rather than all major PDs as defined by the PD Guidance Plan. These major PDs were identified during blinded data review. This change is made to have a more meaningful PPS focusing on primary and key secondary endpoints and to avoid exclusion of subjects with deviations that do not impact the primary or key secondary efficacy assessments.

2. Presentation for actual treatment

The definition of actual treatment for subjects who received incorrect treatment different from their randomized treatment was reaffirmed during the data review meeting. In the safety analyses, a subject will be classified as part of the K-161 group in accordance with SAP Sections 4.4.3 and 4.4.5 if they were initially assigned to the placebo group but received at least one kit of the K-161 treatment. For other treatment errors, the actual treatment group will match the randomized treatment unless a subject was initially allocated to the K-161 group but received placebo treatment kits throughout the study. These decisions are based on the understanding that one kit is used for 3 weeks of treatment.

3. Modifying Race classifications

Race (see SAP Section 6.1) will be handled according to CDISC SDTM terminology like below.

Race as collected	CDISC SDTM terminology
White	White
Black or African American	Black or African American
American Indian or Alaska Native	American Indian or Alaska Native
Asian Indian	Asian
Chinese	
Filipino	
Japanese	
Korean	
Vietnamese	
Other Asian	
Native Hawaiian	Native Hawaiian or Other Pacific Islander
Guamanian or Chamorro	
Samoan	
Other Pacific Islander	
Not reported	Not reported
Unknown	Unknown
Other	Other

4. Number of days of rescue medications and artificial tears

When the start date or the stop date is missing entirely, it will be left missing. When the start and stop dates are partially missing, they will be imputed for the prior [redacted] usage, as defined in SAP Section 7.3, in the following manner:

For partially missing start dates:

- If the year is provided but the month is missing, the month will be set to January.
- If both the month and year are provided but the day is missing, the day will be set to the first day of the month.

For partially missing stop dates:

- If the year is provided but the month is missing, the month will be set to December.
- If both the month and year are provided but the day is missing, the day will be set to the last day of the month.
- If the imputed date falls later than three days before Visit 1, the day will be set to three days before Visit 1.

The number of days of artificial tear and rescue medication usage, as described in SAP Sections 7.3 and 8.4, will be calculated as the sum of days if a patient has multiple medication records. The calculation will encompass the entire duration, considering the earliest start date to the latest end date, particularly in cases where there is an overlap between the specified periods.

5. Dose frequency of [redacted]

The dose frequency of [redacted] collected in the electronic data capture was reviewed during the blinded data review, in accordance with SAP Sections 7.3 and 8.4. The number of doses per day will be calculated based on the following table, which will then be used to determine the total number of doses by multiplying it with the number of days.

Frequency as collected	Corresponding number of doses per day
QH = every hour	16 doses/day (considering 16 hours awake)
Q2H = every 2 hours	8 doses/day (considering 16 hours awake)
Q3H = every 3 hours	5.33 doses/day (considering 16 hours awake)
Q4H = every 4 hours	4 doses/day (considering 16 hours awake)
2 times/week	2 doses/7 days = 0.29 doses/day
3 times/week	3 doses/7 days = 0.43 doses/day
3-4 times/week	3.5 doses/7 days = 0.5 doses/day
3-5 times/week	4 doses/7 days = 0.57 doses/day
5 times/week	5 doses/7 days = 0.71 doses/day
Q2W = every 2 weeks	1 dose/14 days = 0.07 doses/day
Q6M = every 6 months	1 dose/182.625 days = 0.01 doses/day

6. Treatment compliance

Compliance will be considered as missing if the numerator or denominator in SAS Section 7.7.2 is not calculated due to missing data.

7. Statistical approach for primary efficacy endpoints

Originally, two statistical approaches were planned, namely multiple imputation (as outlined in SAP Section 8.1.2) and control-based mean imputation (as described in SAP Section 8.1.4). The former approach was planned to switch the latter one if there were not enough patients to develop imputation models. The decision to use the latter approach for the primary analyses was made based on the results of the data review meeting, which determined the final approach: control-based mean imputation.

8. Typo in the SAS code

From the formula in SAP Section 8.1.4:

$$\hat{V}\left(\hat{\delta}_{new}[c]\right) = \left[A_2 + \left(f_2^{k=1}\right)^2\right]\left(\hat{V}_2^{k=1} + \hat{V}_{1,MAR}\right) + \left[A_2\left(\hat{\mu}_2^{k=1} - \hat{\mu}_{1,MAR} - c\right)^2\right],$$

the sign is modified from "+" to "-" in the code in SAP Section 8.1.4 as follows:

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V_delta_new_c= (A2 + (f2_k1)**2)*(V2_k1 + V1_MAR) + (A2*(mu2_k1 - mu1_MAR - c)**2);
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Final programs have been corrected to reflect this.

9. Range of conservative values (c) for sensitivity analysis in SAP Section 8.1.6

The following ranges of c will be defined to find the tipping point c_t:
- Eye dryness score (visual analog scale): 0 to (100 - $\hat{\mu}_{1,MAR}$),
- Conjunctival sum fluorescein staining score: 0 to (24 - $\hat{\mu}_{1,MAR}$).